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REVIEW

Antenatal Optimization of Maternal Anemia Leads to Decreased Risks of Maternal Morbidity

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Abstract

Purpose of Review Our review focuses on the appropriate use of intravenous iron to increase the likelihood of achieving target hemoglobin levels prior to delivery to reduce maternal morbidity.

Recent Findings Iron deficiency anemia (IDA) is a leading contributor to severe maternal morbidity and mortality. Prenatal treatment of IDA has been demonstrated to reduce the likelihood of adverse maternal outcomes. Recent investigations of intravenous iron supplementation have demonstrated superior efficacy and high tolerability for the treatment of IDA in the third trimester, compared against oral regimens. However, it is unknown whether this treatment is cost-effective, available to clinicians, or acceptable to patients.

Summary Intravenous iron is superior to the oral treatment of IDA; however, its use is limited by the lack of implementation data.

Keywords Iron deficiency anemia · Maternal morbidity · Intravenous iron · Oral iron · Transfusion

Introduction

Background

Anemia is defined as a lower level of hemoglobin in the blood at or below the 5th percentile compared to a healthy pregnant reference population [1••]. Anemia is a common condition in pregnancy with leading causes including physiologic dilution of pregnancy, inherited hemoglobinopathies, acute blood loss, and iron-deficiency anemia. Per the World Health Organization, half of anemia in pregnancy is secondary to iron deficiency. Iron deficiency anemia is defined by a ferritin level of less than 30 mg/dL and varies in severity as stratified by hemoglobin level in Table 1. The likelihood of anemia increases with advancing gestational age with up to 30% of parturients having iron deficiency anemia in the third trimester [2]. The prevalence of anemia is a significant public health indicator due to its association with significant health outcomes and underlying chronic disease [3•]. A 2015 Cochrane review demonstrated that the use of iron supplementation reduced iron deficiency anemia in pregnancy by 57% [4]. Anemia has been associated with severe maternal morbidity including maternal death, antepartum and postpartum thrombosis, transfusion during labor and the postpartum period, hysterectomy, ICU admission, and postpartum hemorrhage [5••]. Therefore, the identification and treatment of iron deficiency anemia are critical for reducing maternal morbidity. This review focuses on the screening and treatment of pregnant patients with iron-deficiency anemia.

Populations at Risk of Iron-deficiency Anemia

There is an increased likelihood of iron deficiency anemia with advancing gestation as previously described when the growing fetus will take substantially more iron stores from the parturient [6]. Populations at increased risk of iron deficiency anemia include teenage mothers, non-Hispanic Black pregnant women, Mexican–American pregnant women, and multiparous women with a parity greater than 2 or those with a short interval pregnancy of less than 12 months [2, 7]. Women who have a diet deficient in iron-rich foods [e.g., beef, shrimp, beans, lentils], iron-enriched breakfast cereals, or a diet deficient in iron-enhancers [e.g., orange or grapefruit juice, peppers, broccoli] may additionally influence iron stores [1••, 2].

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Table 1 Definition of iron deficiency anemia

Iron deficiency anemia Anemia secondary to depleted iron stores with ferritin less than 30 ng/mL	
Mild	Hemoglobin 10–11 g/dL or Hematocrit 30–33%
Moderate	Hemoglobin 8.5–10 g/dL or Hematocrit 25.5–30%
Severe	Hemoglobin < 8.5 g/dL or Hematocrit < 25.5%

Screening for Anemia

Universal screening at two distinct times during pregnancy is advised by the American College of Obstetricians and Gynecologists (ACOG) [1••]. A complete blood count to assess the red blood count is advised in the first trimester and again at 24 0/7–28 6/7 weeks' gestation. If the hemoglobin is less than 10 g/dL, a systematic approach to assessing the etiology for the anemia is advised to include screening for sickle cell anemia, thalassemias, and iron-deficiency anemia; further screening may be indicated based on classification by microcytic, normocytic, or macrocytic anemia [1••] or clinical risk factors.

Historically, ACOG has suggested using different thresholds for the diagnosis of anemia among Black and non-Black women. They recommended using a cutoff for anemia with hemoglobin < 10.2 g/dL in Black women and < 11.0 g/dL in non-Black women. However, this increases the risk of Black women presenting with high rates of anemia at the time of delivery and increased rates of blood transfusion after delivery [8]. Given this, standardized definitions for all patients are recommended when diagnosing anemia in clinical practice.

Assessment of Iron-deficiency Anemia

Given the frequency of iron-deficiency anemia, a hematocrit or hemoglobin is an appropriate screening test for iron-deficiency anemia. Diagnosis of IDA requires demonstration of depleted iron plasma levels, iron stores, high total iron-binding capacity, low ferritin levels, or increased levels of free erythrocyte protoporphyrin. A ferritin level has the highest sensitivity and specificity of assessing for iron-deficiency anemia (Fig. 1). In pregnancy, levels of less than 30 mg/L are consistent with a diagnosis of iron deficiency anemia [1••].

Another potential biomarker, hepcidin, has recently been evaluated as an indicator for pregnant individuals who will appropriately respond to iron supplementation. Hepcidin is suppressed in the setting of iron deficiency and increased in the setting of high plasma iron. Hepcidin decreases intestinal absorption of oral iron, and therefore, higher levels of hepcidin reflect individuals who will poorly respond to iron supplementation. A well-designed randomized controlled trial assessed the use of hepcidin into an algorithm to assess treatment effectiveness with oral iron and did not demonstrate any difference in hemoglobin levels [9].

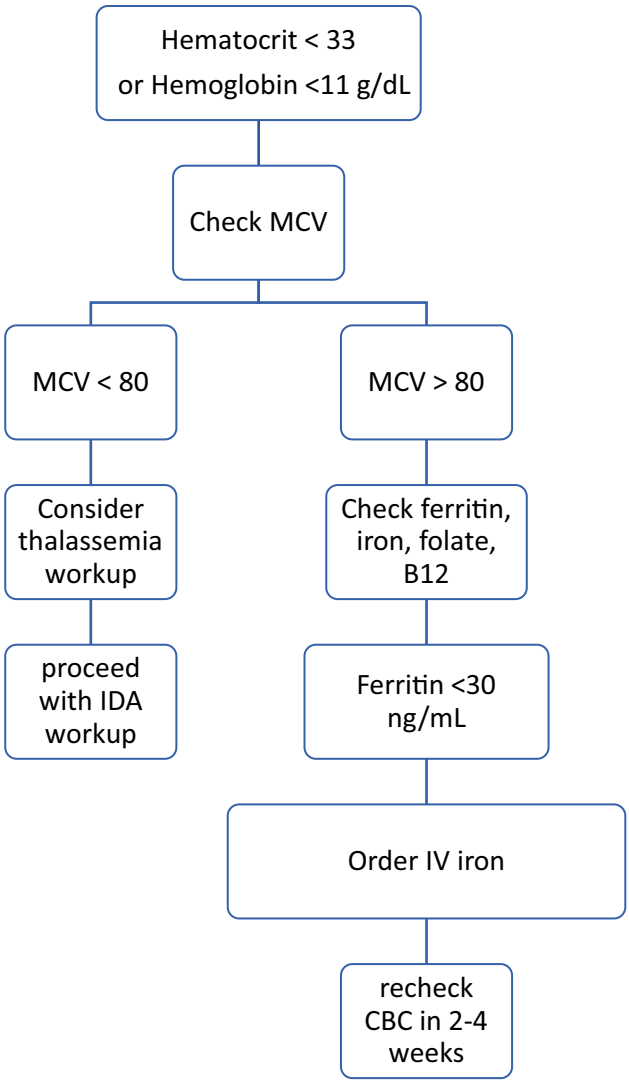

Fig. 1 Algorithm for evaluation and treatment of anemia for inpatient pregnant patients

Outcomes Associated with Antepartum Anemia

Pregnancies complicated by iron deficiency anemia have a higher likelihood of both maternal and neonatal morbidity. Pregnant individuals with iron deficiency anemia are at higher risk of severe maternal morbidity including maternal death, antepartum and postpartum thrombosis, transfusion during labor and the postpartum period, hysterectomy, intensive care unit admission, and postpartum hemorrhage [5••]. A large study of 166,566 deliveries in the USA found that 10,217 (6.1%) pregnant individuals were diagnosed with anemia. Pregnancies with anemia demonstrated a 2.04-fold

increased rate of a composite maternal morbidity including maternal death, eclampsia, thrombosis, transfusion, hysterectomy, and maternal ICU admission compared to non-anemic individuals. The rates of postpartum transfusion for anemic individuals (6.9%) were nearly two-fold higher ($P < 0.001$) compared to individuals without anemia (3.7%) [5••]. There were no differences in neonatal birthweight, neonatal anemia, or transfusion between anemic and non-anemic parturients [5••].

Treatment of Iron Deficiency Anemia

Iron supplementation is recommended for any pregnant patient with a diagnosis of iron-deficiency anemia. In pregnancy, women need higher levels of daily elemental iron intake compared to the general population in order to accommodate the fetal and placental blood volume and the increased maternal red blood cell volume in pregnancy [10]. A typical prenatal vitamin contains 27 mg of elemental iron which is just below the recommended 30 mg of elemental iron intake for a pregnant woman.

Patients diagnosed with iron-deficiency anemia will require additional iron intake above the iron supplementation of a daily prenatal vitamin or dietary intake. The Centers for Disease Control (CDC) and ACOG recommend additional iron intake. Patients who may not be appropriate candidates for iron supplementation include patients with hemochromatosis, sickle cell anemia, or polycythemia vera as these conditions may be adversely exacerbated by iron supplementation.

Oral Iron Treatment

Oral iron is the first-line treatment for mild-moderate iron deficiency anemia in pregnancy [1••]. However, there are many limitations to oral iron supplementation including low intestinal absorption and a high rate of gastrointestinal side effects [11, 12]. There are many formulations of oral iron including ferrous fumarate, ferrous gluconate, and ferrous sulfate. The rate of intestinal iron absorption is low but increases throughout pregnancy. The rate of iron absorption in pregnancy was demonstrated to be 7% in the first trimester and 14% in the late third trimester attributed to a higher rate of intestinal absorption as iron stores became more depleted throughout pregnancy [12, 13]. The likelihood of gastrointestinal adverse reactions such as nausea, vomiting, epigastric discomfort, diarrhea, and constipation may be as high as 31–47% [11].

Intravenous Iron Treatment

Intravenous iron is recommended for pregnant individuals who have severe iron deficiency in the later aspect of pregnancy or those that cannot tolerate oral iron [1••, 16]. Intravenous iron avoids intestinal absorption and has been demonstrated to have higher maternal hemoglobin at delivery, fewer adverse medication reactions, and a greater likelihood of achieving target hemoglobin compared to oral iron treatments [1••, 14, 15•, 16, 17]. A recent systematic review found pregnant individuals with iron deficiency anemia receiving intravenous iron compared to oral iron had a statistically reduced (OR 0.35; 95% CI 0.18–0.67) likelihood of adverse reactions and an increased hemoglobin level after 4 weeks of treatment [14]. A randomized controlled trial of 38 patients with iron deficiency anemia demonstrated a statistically increased likelihood of successful treatment of anemia (hemoglobin > 11) with a single dose of low molecular weight iron dextran compared to oral iron. The trial did not demonstrate a difference in blood transfusions, likely secondary to the smaller trial size [15•].

The challenges of receiving intravenous iron include the necessary intervention of intravenous access, the need for administration in a monitored setting, the duration of the infusion, and possibly the need for multiple infusions depending on the prescribed iron formulation and the travel time necessary to get to an office setting. In the randomized trial previously described, 10 of 38 individuals assigned to intravenous iron declined due to logistic reasons, and 27.8% of the individuals randomized to a particular iron treatment elected to pursue a different iron treatment outside of the research study indicating that women may have had strong underlying preferences of preferred iron treatments. In this trial, the researchers specifically utilized an intravenous iron formulation that can deliver the full iron dose with only one infusion unlike other formulations (such as iron sucrose) as another randomized controlled trial utilized iron sucrose with participants receiving a varying number of infusions despite research intentions for the same dosing [18]. More than one iron infusion may be more logistically or financially challenging to obtain than a solitary iron infusion. Intravenous iron often requires additional coordination with outpatient infusion or hematology clinics. In the midst of the COVID-19 pandemic and associated staffing shortages, access to these facilities may be impacted.

Providers should aim for a target hemoglobin of at least 10 g/dL or a higher target in anticipation of delivery for pregnant women who may have a religious or ethical objection to blood transfusion or are at higher risk of postpartum hemorrhage. A month after treatment has concluded, a repeat assessment of the hemoglobin is advised [1••]. Formulations of intravenous iron are outlined in Table 2 describing dosing, the need for repeat infusions, and risks of adverse reactions. The risk of adverse reaction to intravenous iron is fortunately low although there are documented risks of allergic reactions and adverse outcomes (Table 2). Prior formulations now not available in the USA (high molecular

Table 2 Intravenous iron formulations and standard dosing [20, 21]

Intravenous iron formulation	Dose	Doses for iron deficit of 1000 mg	Possible adverse reactions	Duration of infusion	Test dose required
Ferric carboxymaltose	750 mg	2	Erythema Palpitations Dizziness Headache Neck spasm Face Flushing Nausea, vomiting Diarrhea Injection site pain Headache Hypotension Anaphylaxis 0.1%	< 1 h	No
Ferric derisomaltose	1000 mg	1		< 1 h	No
Ferumoxytol	1020 mg	1		< 1 h	No
Iron sucrose	200–300 mg	4–5		< 1 h	No
Low molecular weight iron dextran	1000 mg	1		1 h	Yes
Ferric Gluconate	250 mg	4		1 h	No

weight iron dextran) resulted in a higher incidence of anaphylaxis and other severe allergies; the risk of anaphylaxis to low molecular weight iron dextran is fortunately quite rare at 1 in 200,000 [19].

The ideal treatment for iron deficiency anemia and treatment effects remain an ongoing research interest within obstetrics. Various protocols have been proposed for the identification and treatment of anemia in pregnancy. At our institution, we have adopted the protocol in Fig. 1 for patients admitted to our antepartum unit. Additional protocols suggest that if patients are unresponsive to oral iron after a 4-week interval then strong consideration should be made towards IV iron formulations or if iron deficiency anemia is diagnosed at > 34 weeks' gestation.

Effect of Appropriate Treatment in Reducing Maternal Risk

As noted previously, anemia is associated with various maternal morbidities including blood transfusion, ICU admission, and postpartum hemorrhage [1••].

Multiple studies indicate that supplemental use of iron in all pregnancies results in a subsequent increase in hemoglobin and ferritin by the time of delivery [14, 15•, 22]. Furthermore, a meta-analysis of 48 randomized controlled trials and 44 cohort studies demonstrates that iron supplementation in all pregnancies has a linear dose-response increase in neonatal birthweight; there was no significant effect on preterm birth or the likelihood of small for gestational age neonates [22]. In a meta-analysis of twenty studies including 1359 women receiving intravenous iron and 1357 women receiving oral iron during pregnancy, outcomes assessing maternal hemoglobin and ferritin at delivery in addition to transfusion rates were reviewed [15•]. Intravenous iron was associated with increased maternal hemoglobin and ferritin at delivery as well as birthweight and neonatal ferritin. There was limited data on blood product transfusion and mode of delivery outcomes.

A subsequent retrospective study of 5054 patients compared women who received oral iron to those who received intravenous iron at a median gestational age of 33 weeks' gestation [17]. Those receiving intravenous iron were more likely to have severe anemia; those receiving intravenous iron had a higher median increase of hematocrit from nadir to admission for delivery. The median number of intravenous doses of iron in this study was 4.5, and the median hematocrit increase with intravenous iron supplementation was 4.5%. The study found that when controlling for confounders, there was a statistically significant higher likelihood of composite maternal morbidity in those receiving intravenous iron; however, this was seen only in the subset of patients who had not completed their intravenous iron treatment (less than 5 doses). This suggests that for individuals with severe iron deficiency anemia, intravenous iron can result in a higher median rise in hematocrit compared to those treated without intravenous iron. There was no difference in the rate of blood transfusions [17]. Women receiving more than 5 doses of intravenous iron were more likely to have private insurance, be married, receive a diagnosis earlier in gestation, and have advanced maternal age compared to women receiving less than 5 intravenous iron doses in pregnancy [17].

Alternative Treatments: Erythropoietin

There is a subset of patients with non-responsive iron-treated anemia who may benefit from erythropoietin (EPO) supplementation. Erythropoietin is a hormone produced by the kidneys that stimulated red blood cell production [23•, 24]. The use of EPO is more widespread in non-pregnant patients diagnosed with transfusion-dependent end-stage renal disease compared to pregnant individuals. Synthetic EPO also known as erythropoietin stimulating agents (ESAs) function by stimulation of erythroid progenitor cells that creates a downstream effect causing an increase in hemoglobin and hematocrit [24]. The medications have been reported to be well tolerated with rare side effect profiles including hypertension, venous thromboembolism, and ischemic stroke.

This treatment was initially used in pregnant patients with dialysis-dependent kidney disease; however, studies have further evaluated its use in iron deficiency anemia in pregnancy [25]. In these studies, recombinant human erythropoietin (rHuePo) was used in conjunction with iron to determine the improvement of anemia. A randomized controlled trial demonstrated an increase in hemoglobin after 4 weeks when 4000 units of adjuvant recombinant human erythropoietin were combined with oral iron supplementation compared to oral iron supplementation alone (1.92 g/dL versus 2.33 g/dL *p*-value 0.013) [26]. The groups were randomized at a mean of 33 weeks' gestation. The authors reported no change in fetal or neonatal hematologic parameters. Recombinant human erythropoietin does not cross the placenta due to the large molecular size, and therefore, fetal effects are expected to be minimal [18]. Future studies evaluating any maternal complications including pregnancy-induced hypertension, preterm delivery, and venous thromboembolism events need to be further elucidated.

In Europe, the Network for the Advancement of Patient Blood Management, Haemostasis, and Thrombosis (NATA) and the International Federation of Gynaecology and Obstetrics (FIGO) suggest that for patients unresponsive to IV iron supplementation or those who decline blood transfusion, treatment with ESA should be considered with guidance from hematology [27].

Anemia in the Postpartum Period

There is no clear definition for the diagnosis of postpartum anemia. The Center for Disease Control and Prevention (CDC) suggests that the value should be similar to non-pregnant individuals with a hemoglobin < 11.8 g/dL [12]. European guidelines have recommended values of 10.0–12.0 g/dL [25, 28].

Part of the difficulty in diagnosing postpartum anemia is timing blood count measurements. Postpartum anemia can be a reflection of ongoing antepartum iron deficiency anemia or may reflect recent postpartum blood loss. Furthermore, ongoing hormonal and hemodynamic changes in the postpartum period can alter hemoglobin and hematocrit values. In the postpartum period, there is ongoing iron depletion of 0.8 mg/day due to obligatory loss and 0.3 mg/day due to lactational losses [29]. The utility of universal screening in the postpartum period is likely low; however, for patients at risk for postpartum anemia, a complete blood count level drawn 24–48 h after delivery can be considered.

The treatment options in the postpartum period remain the same as antenatal options. Patients should be offered oral iron, IV iron, erythropoietin, or autologous blood transfusion based on the clinical situation and severity of anemia. In a systematic review of 2182 patients receiving oral or IV iron, authors found that those who received IV iron postpartum had higher hemoglobin values at 6 weeks postpartum compared to those who received oral iron [30]. The authors also found that in a large portion of the study participants, ferritin values were significantly improved for those who received IV iron postpartum [30].

We recommend that for patients with mild anemia (hemoglobin < 11.0 g/dL) that patients are offered oral iron repletion after delivery. For patients with moderate to severe anemia (hemoglobin < 9.5 g/dL), patients can be offered IV iron in the immediate postpartum period prior to discharge. Blood transfusion for symptomatic patients with severe anemia can be individualized.

Conclusion

Maternal anemia is implicated in multiple peripartum outcomes including postpartum hemorrhage, blood transfusion, cesarean delivery, and small for gestational age. Prompt recognition and treatment of anemia have been shown to improve hemoglobin and ferritin values by the time of delivery. Future research regarding optimal formulation for iron is still required. Additionally, individual morbidity outcomes need to be explored in future studies to further understand if the treatment of anemia reduces these factors.

Compliance with Ethical Standards

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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